APPENDIX C

Illustrative examples of issued U.S. Patents with claims to pharmaceutical compositions comprising a single specified component

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United States Patent

Patent Number: US 5049563
Date of Patent: 910917

ANNELATED INDOLEKETONES WITH AN IMIDAZOLYLALKYL SUBSTITUENT; 5-HYDROXYTRYPTAMINE RECEPTOR ANTAGONISTS

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Assignee: Duphar International Research BV, NL
Appl. No.: US 374774
Filed: 890703

Related U.S. Application Data

Priority Applic(Ser#,Date): NL 8801714 880707

Int. Cl. A61K-031/435; C07D-221/18
U.S. Cl. 514284000; 514183000; 514214000; 514410000; 540450000; 540576000; 546071000; 548420000
Field of Search 514284000; 546071000; 546094000; 548425000; 548428000

Primary Examiner - Fan, Jane T
Assistant Examiner - Chang, Celia
Attorney, Agent or Firm - Stevens, Davis, Miller & Mosher

ABSTRACT

Annelated indoleketones with an imidazolylalkyl substituent having the formula (2):

D R A W I N G

wherein R1 is alkyl or alkoxy having 1-4 C-atoms, hydroxy, halogen, trifluoromethyl, a group R5R6N or R5R6-N-CO, wherein R5 and R6 are hydrogen or alkyl having 1-4 C-atoms or wherein R5R6N is a saturated 5-6 ring, and n has the value 0, 1 or 2; A is a group of formula 3, 4 or 5

D R A W I N G

wherein one of the groups R2, R3 and R4 is hydrogen, alkyl having 1-4 C-atoms, cycloalkyl having 3-6 C-atoms or alkenyl having 2-4 C-atoms and the two other groups, independently of each other, are hydrogen or alkyl having 1-4 C-atoms, p has the value 0-3, and q has the value 2-5. These compounds (and pharmaceutically acceptable acid addition salts thereof) have good antagonistic activity of ''neuronal'' 5hydroxytryptamine(5-HT)receptors, and the lower toxicity.
003 Claims

EXEMPLARY CLAIM

1. Compounds of formula (2):

4,5-(-(CH2)p-CH(-CH2-A)-CO-),(R1)n-1,2,3,4-TETRAHYDRO-PYRIDO(1,2-a)INDOLE (2)

wherein R1 is alkyl or alkoxy having 1-4 C-atoms, hydroxy, halogen, trifluoromethyl, a group R5R6N or R5R6-N-CO, wherein R5 and R6 are hydrogen or alkyl having 1-4 C-atoms or wherein R5R6N is a saturated 5-6 membered ring, and n has the value 0, 1 or 2; A is a group of formula 3, 4 or 5

2-R2,4-R3,5-R4-IMIDAZOL-1-YL, (3)
1-R3,2-R4,5-R2-IMIDAZOL-4-YL, (4)
1-R3,2-R4,4-R2-IMIDAZOL-5-YL, (5)

wherein one of the groups R2, R3 and R4 is hydrogen, alkyl having 1-4 C-atoms, cycloalkyl having 3-6 C-atoms or alkenyl having 2-4 C-atoms and the two other groups, independently of each other, are hydrogen or alkyl

having 1-4 C-atoms, has the value 0-3, and pharmaceutically acceptable acid addition salts thereof.

3. A method of preparing pharmaceutical compositions wherein as active ingredient a compound of formula (2) as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, is admixed with a solid or liquid carrier.

NON-EXEMPLARY CLAIMS

2. Pharmaceutical compositions useful as antagonists of neuronal 5-hydroxytryptamine receptors, and which comprise at least one compound as claimed in claim 1 as an active substance.

United States Patent

Patent Number: US 4874770
Date of Patent: 891017

ARYL-SUBSTITUTED (N-PIPERIDINYL)METHYL- AND (N-PIPERIDINYL) METHYLAZOLES HAVING ANTIPSYCHOTIC PROPERTIES

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Assignee: Duphar International Research BV, Weesp, NL
Appl. No.: US 214310
Filed: 880701

Related U.S. Application Data

Division of(Pat#,Ser#,Date): US 4772604 US 18164 870224
Priority Applic(Ser#,Date): NL 8600488 860227
Int. Cl. A61K-031/445; C07D-211/10; C07D-211/14
U.S. Cl. 514326000; 546208000
Field of Search 514326000; 546208000; 546210000

Primary Examiner - Shen, Cecilia
Attorney, Agent or Firm - Stevens, Davis, Miller & Mosher

ABSTRACT

The invention relates to new aryl-substituted (Npiperidinyl)methyl- and (N-piperazinyl)methylazoles having interesting pharmacological, notably antipsychotic, properties. The compounds may be prepared in a manner known for the synthesis of analogous compounds and be processed to compositions according to known methods.
004 Claims

EXEMPLARY CLAIM

1. COMPOUNDS OF FORMULA 1

((R)N-PHENYL)-A-CH(-R1)-N<(-CH(-R2)-CH2-X(-R4)-CH2- CH(-R3)-) (I)

IN WHICH THE SYMBOLS HAVE THE FOLLOWING MEANINGS: R IS METHYL, METHOXY OR HALOGEN; N IS 0-2; R1, R2 AND R3 ARE HYDROGEN; X IS A CARBON ATOM WHICH IS SUBSTITUTED WITH A GROUP R5, IN WHICH R5 IS HYDROGEN OR HYDROXYL; R4 IS PHENYL OR BENZOYL, WHICH MAY BE SUBSTITUTED WITH HALOGEN OR METHOXY; A IS PYRROLE OR PYRAZOLE, WHICH MAY BE SUBSTITUTED WITH METHYL OR PHENYL; AND THE ACID ADDITION SALTS AND PRODRUGS THEREOF.

4. A METHOD OF TREATING AFFECTIONS IN THE CENTRAL NERVOUS SYSTEM, CHARACTERIZED IN THAT AN EFFECTIVE AMOUNT OF A COMPOUND AS CLAIMED IN CLAIM 1 IS USED.

NON-EXEMPLARY CLAIMS

2. Compounds as claimed in claim 1: (r) 1-(5-(4-fluorophenyl)pyrrol-2-yl) methyl-4-(4-fluorobenzoyl)piperidine; (s) 1-(1-phenylpyrazol-4-yl)methyl -4-(4-fluorobenzoyl)piperidine; and (t) 1-(5(3)-phenylpyrazol-3-(5)-yl)m ethyl-4-(4-fluorobenzolyl)piperidine.
3. Pharmaceutical compositions which comprise at least an effective amount of one compound as claimed in claim 1 as the active substance.

United States Patent

Patent Number: US 4772604
Date of Patent: 880920

PHENYL-SUBSTITUTED (N-PIPERAZINYL) METHYLAZOLES FOR TREATING AFFECTIONS IN THE CENTRAL NERVOUS SYSTEM; ANTIPSYCHOTIC AGENTS

Inventor(s): van der Heyden, Johannes A M, Weesp, NL; van Wijngaarden, Ineke, Weesp, NL; Kruse, Cornelis G, Weesp, NL; Tulp, Martinus T M, Weesp, NL
Assignee: Duphar International Research BV, Weesp, NL
Appl. No.: US 18164
Filed: 870224

Related U.S. Application Data

Priority Applic(Ser#,Date): NL 8600488 860227

Int. Cl. A61K-031/495; C07D-403/06
U.S. Cl. 514252000; 514253000; 544359000; 544371000; 544372000; 544377000
Field of Search 514252000; 514253000; 544359000; 544371000; 544372000; 544377000

Primary Examiner - Daus, Donald G
Assistant Examiner - Shen, Cecilia
Attorney, Agent or Firm - Stevens, Davis, Miller & Mosher

ABSTRACT

The invention relates to new aryl-substituted (Npiperidinyl)methyl- and (N-piperazinyl)methylazoles having interesting pharmacological, notably antipsychotic, properties. The compounds may be prepared in a manner known for the synthesis of analogous compounds and be processed to compositions according to known methods.
003 Claims

EXEMPLARY CLAIM

1. COMPOUNDS OF FORMULA (1):

((R)N-PHENYL)-A-CH(-R1)-N<(-CH(-R2)-CH2-X(-R4)-CH2CH(-R3)-) 1

IN WHICH THE SYMBOLS HAVE THE FOLLOWING MEANINGS: R IS ALKYL, HYDROXYALKYL, ALKOXY OR ALKYLTHIO HAVING 1-3 CARBON ATOMS, NITRO, HALOGEN, TRIFLUOROMETHYL, OR ALKYLSULPHONYL HAVING 1-3 CARBON ATOMS; N HAS THE VALUE 0-2; R1, R2 AND R3 INDEPENDENTLY OF EACH OTHER REPRESENT HYDROGEN OR METHYL; X IS A NITROGEN ATOM; R4 IS PHENYL, BENZOFURANYL, BENZODIOXANYL, BENZODIOXEPANYL OR BENZOYL, WHICH GROUPS MAY BE SUBSTITUTED WITH A GROUP (R)N, WHEREIN R AND N HAVE THE ABOVE MEANINGS; AND A IS A PYRROLE RING OR A PYRAZOLE RING, WITH THE PROVISO THAT THE PHENYL GROUP IS IN THE META POSITION WITH RESPECT TO THE ALKYLAMINO SUBSTITUENT, WHICH RINGS MAY BE SUBSTITUTED WITH METHYL OR WITH A PHENYL GROUP WHICH MAY BE SUBSTITUTED WITH A GROUP (R)N, AND WITH PHARMACOLOGICALLY ACCEPTABLE ACID ADDITION SALTS THEREOF.

NON-EXEMPLARY CLAIMS

2. Compounds as claimed in claim 1: (a) 1-(5-(3-chlorophenyl)pyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (b) 1-(5-phenylpyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (c) 1-(5-(2,6-dichlorophenyl)pyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (d) 1-(5-phenylpyrrol-2-yl)methyl-4-(2-methoxy-4-fluorophenyl)piperazine; (e) 1-(5-(2,6-difluorophenyl)pyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (f) 1-(5-(4-fluorophenyl)pyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (g) 1-(5-(2-methoxyphenyl)pyrrol-2-yl)methyl-4-(2-methoxyphenyl)piperazine; (h) 1-(5-(4-fluorophenyl)pyrrol-2-yl)methyl-4-(4-fluorophenyl)piperazine; (i) 1-(5-(4-fluorophenyl)pyrrol-2-yl)methyl-4-(3-trifluoromethylphenyl)piperazine; (j) 1-(5-(4-fluorophenyl)pyrrol-2-yl)methyl-2-methyl-4-(2-methoxyphenyl)pipe

razine; (k) 1-(5-(4-fluorophenyl)pyrrol-2-yl)methyl-4-(benzo(b)furan-7-yl)piperazine; (l) 1-(5-phenylpyrrol-2-yl)methyl-4-(2H-3,4-dihydrobenzo-1,5-dioxepin-6-yl)piperazine; (m) 1-(5-phenylpyrrol-2-yl)methyl-4-((3-hydroxymethyl)-benzo-1,4-dioxan-5-yl)piperazine; (n) 2-(5(3)-phenylpyrazol-3(5)-yl)methyl-4-(2-methoxyphenyl)piperazine; (o) 1-(1-phenylpyrazol-4-yl)methyl-4-(2-methoxyphenyl)piperazine; or (u) 1-(5(3)-(4-fluorophenyl)pyrazol-3(5)-yl)methyl-4-(2-methoxyphenyl)piperazine.

3. Pharmaceutical compositions which comprise at least one compound as claimed in claim 1 as the active substance.

United States Patent

Patent Number: US 5086065
Date of Patent: 920204

PHENYLALKAN(EN)OIC ACID; LEUKOTRIENE ANTAGONISTS

Inventor(s): Hamanaka, Nobuyuki, Osaka, JP; Konno, Mitoshi, Osaka, JP; Nakae, Takahiko, Osaka, JP
Assignee: Ono Pharmaceutical Co, Ltd, Osaka, JP
Appl. No.: US 524521
Filed: 900517

Related U.S. Application Data

Priority Applic(Ser#,Date): JP 89164213 890627
JP 89310545 891201
JP 901799 900109

Int. Cl. A61K-031/425; C07D-275/03
U.S. Cl. 514372000; 544003000; 548214000
Field of Search 514372000; 548214000

Primary Examiner - Ford, John M
Attorney, Agent or Firm - Sughrue, Mion, Zinn Macpeak & Seas

ABSTRACT

The phenylalkan(en)oic acids of the formula:

D R A W I N G

wherein A is i) -NHCO-, ii) -Oiii) -NHSO2-, iv) -COv) -CH2- or vi) -CH(OH)-; W is i) C1-13 alkylene, ii) phenylene or iii)

D R A W I N G

R1 is i) hydrogen, ii) C1-4 alkyl, iii) -COOH, iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom or saturated or unsaturated, 4-7 member mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group, v)

D R A W I N G

vi) -CH2OH; or A, taken together with W and R1, is i)

D R A W I N G

ii)

D R A W I N G

iii) -N-(SO2R6)2, iv)

D R A W I N G

or v)

D R A W I N G

two R2 are, same or different, i) hydrogen, ii) C1-4 alkyl or iii) 4-7 membered saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total, or two R2, taken together with a nitrogen to which they are attached, form saturated or unsaturated, i) 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or ii) 4-7 mebered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total; Y is ethylene or vinylene; D is i) -Z-B or ii)

D R A W I N G

Z is C3-11 alkylene or alkenylene R is

D R A W I N G

or Z taken together with B, is C3-22 alkyl; R3 is i) hydrogen, ii) halogen, iii) C1-8 alkyl, alkoxy or alkylthio, or iv) C2-8 alkenyl, alkenyloxy or alkenylthio; n is 1-3; R4 is C1-7 alkylene; R5 is i) C1-12 alkyl, ii) C2-12 alkenyl, iii) C5-7 cycloalkyl or pp2 iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy; Two R6 are, same or different, i) C1-7 alkyl, ii) benzyl or iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and Two R7 are, same or different, C1-4 alky; with the proviso that i) -A-W-R1 should bind to 3- or 4- carbon in benzene ring, and ii) when W phenylene or

D R A W I N G

A should not represent -O-, -CO-, -CH2- or -CH(OH)-; and nontoxic salts thereof, possess an antagonistic activity on leukotriene B4, and therefore, are useful for the prevention and treatment of several diseases induced by leukotriene B4.

004 Claims

EXEMPLARY CLAIM

1. A phenylkan(en)oic acid of the formula:

1-(D-O-),2-(HOOC-Y-),(R1-W-A-)BENZENE I

wherein A, taken together with W and R1, is i)

(1,1,3-TRI(O=)ISOTHIAZOLIDIN-2-YL)-,

Y is ethylene or vinylene; D is i) -Z-B or ii)

-R4-CH=CH-CH(-OH)-R5;

Z is C3-11 alkylene or alkenylene B is

(((R3)n-)PHENYL)-;

or Z, taken together with B, is C3-22 alkyl; R3 is i) hydrogen, ii) halogen, iii) C1-8 alkyl, alkoxy or alkylthio or iv) C2-8 alkenyl, alkenyloxy or alkenylthio; n is 1-3; R4 is C1-7 alkylene; R5 is i) C1-12 alkyl, ii) C2-12 alkenyl, iii) C5-7 cycloalkyl or iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy; with the proviso that -A-W-R1 should bind to 3- or 4- carbon in benzene ring and non-toxic salts thereof.

NON-EXEMPLARY CLAIMS

2. A compound according to claim 1, which is 3-(1-(6-(4-methoxyphenyl)hex-5E-enyl)oxy-4-(isothiazolidin-1,1,3-trione-2-yl)benzen-2-yl)propionic acid.
3. A pharmaceutical composition for diseases induced by leukotrien B4 which comprise, as active ingredient, an effective amount of the phenylalkan(en)oic acid of the formula (I) as claimed in claim 1, or the pharmaceutically acceptable acid addition salts thereof.
4. A method for the prevention and treatment of several diabetic complications, diseases induced by leukotriene B4, which comprises the administration of an effective amount of the phenylalkan(en)oic acid of the formula (I) as claimed in claim 1, or the pharmaceutically acceptable acid addition salts thereof

United States Patent

Patent Number: US 5037844
Date of Patent: 910806

SUBSTITUTED 1H-INDAZOLE-3-CARBOXAMIDES; 5-HYDROXYTRYPTAMINE ANTAGONIST

Inventor(s): van Wijngaarden, Ineke, Weesp, NL; Hamminga, Derk, Weesp, NL
Assignee: Duphar International Research BV, Weesp, NL
Appl. No.: US 554918
Filed: 900720

Related U.S. Application Data

Priority Applic(Ser#,Date): NL 8901917 890725

Int. Cl. A61K-031/415; C07D-487/00
U.S. Cl. 514394000; 548311700
Field of Search 514394000; 548327000
Primary Examiner - Lee, Mary C
Assistant Examiner - McKane, Joseph K
Attorney, Agent or Firm - Stevens, Davis, Miller & Mosher

ABSTRACT

The present invention is concerned with compounds of formula 1:

D R A W I N G

wherein R1 is straight or branched alkyl having 1-4 C-atoms, halogen or cyano; n has the value 0-1; R2 is hydrogen, (1-6 C)alkyl, (3-6 C)alkenyl, (3-6 C)alkenyl, (36 C)cycloalkyl, (3-6 C)cycloalkyl-(1-4 C) alkyl, phenyl, phenyl(1-3 C)alkyl, COOR6, COR6, CONR6R7 or SO2-R6, wherein R6 and R7 independently of each other are hydrogen, (1-6 C)alkyl, (3-6 C)cycloalkyl, phenyl or phenyl-(1-4 C)alkyl, wherein the benzene ring is optionally substituted with a methyl group or a halogen atom, with the proviso that R6 is not hydrogen when R2 is a group COOR6 or SO2R6; R3 is hydrogen, straight or branched (1-6 C)alkyl or a phenyl-(13 C)alkyl group optionally substituted in the benzene ring; and A is a group of formula 2 or 3

D R A W I N G

wherein one of the groups R8, R9 and R10 is hydrogen, (1C)alkyl, (3-6 C)cycloalkyl, (3-4 C)alkenyl or (3-4 C)alkynyl and the two other groups, independently of each other, are hydrogen or (1-4 C)alkyl, and the pharmacologically acceptable acid addition salts thereof, which are pharmaceutically useful as strong and selective antagonists of ''neuronal'' 5-hydroxy tryptamine (5-HT) receptors.
003 Claims

EXEMPLARY CLAIM

1. Compounds of formula 1:

(1-R2,(R1)n-INDAZOL-3-YL)-CO-N(-R3)-CH2-A 1

wherein R1 is straight or branched alkyl having 1-4 C-atoms, halogen or cyano; n has the value 0-1; R2 is hydrogen, (1-6 C)alkyl, (3-6 C)alkenyl, (3-6 C)cycloalkyl, (3-6 C)cycloalkyl-(1-4 C)alkyl, phenyl, phenyl-(1-3 C)alkyl, COOR6, COR6, CONR6R7 or SO2-R6, wherein R6 and R7 independently of each other are hydrogen, (1-6 C)alkyl, (3-6 C)cycloalkyl, phenyl or phenyl-(1-4 C)alkyl, wherein the benzene ring is optionally substituted with a methyl group or a halogen atom, with the proviso that R6 is not hydrogen when R2 is a group COOR6 or SO2R6; R3 is hydrogen, straight or branched (1-6 C)alkyl or a phenyl(1-3 C)alkyl group optionally substituted in the benzene ring; and A is a group of formula 2 or 3

(1-R9,2-R10,5-R8-IMIDAZOL-4-YL)- 2

(1-R9,2-R10,4-R8-IMIDAZOL-5-YL)- 3

wherein one of the groups R8, R9 and R10 is hydrogen, (1-4 C)alkyl, (3-6 C)cycloalkyl, (3-4 C)alkenyl or (3-4 C)alkynyl and the two other groups, independently of each other, are hydrogen or (1-4 C)alkyl, or a pharmacologically acceptable acid addition salt thereof.

NON-EXEMPLARY CLAIMS

2. Pharmaceutical compositions which comprise a compound as claimed in claim 1 as the active substance.
3. A method of treating syndromes caused by serotonin, by administering an effective amount of a compound as claimed in claim 1